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Auditory brainstem and cognitive evoked potentials in assessment of brain functional status in patients with ischemic stroke

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Current research aimed to investigate informational content of brainstem acoustic evoked potentials (BAEPs) and auditory cognitive event-related potential — mismatch negativity (MMN) in assessment of brain functional status and cognitive functions in patients with ischemic stroke. MMN is a component of auditory event-related potential with peak latency at 100–250 ms, which reflects automatic process of difference detection between stimuli and neurodynamic processes in auditory cortex at pre-attentive stage. Clinical and neurophysiological examination, including registration of BAEPs and MMN was performed for 22 patients (12 — with ischemic stroke in carotid circulation, 10 — without cerebrovascular diseases). According to results obtained using scales of MMSE, FAB, test with 10 words repetition and Schulte tables, patients with IS demonstrated cognitive impairment as compared to control group. During BAEPs examination, functional changes in brainstem were observed (increased latency of wave V and elongation of interpeak intervals III-V on both sides and III–V ipsilaterally) in patients with ischemic stroke. Also they demonstrated increased peak latency and decreased amplitude of MMN. It points at a decline in auditory discrimination accuracy, shortened lifetime of memory traces and deficit in involuntary attention switching and also indicates of cognitive impairment.

Keywords: ischemic stroke, cognitive impairment, mismatch negativity, acoustic brainstem evoked potentials, auditory evoked potentials.

Cerebral vascular diseases recently are among the main causes of morbidity, invalidism and mortality worldwide. According to WHO statistics, there are 6.7 million cases of fatal stroke annually [1]. According to National Stroke Register, over 400 thousand cases of stroke occur every year in Russia [2]. Cognitive impairment is one of the most serious complications of stroke, developing in 35–83 % of patients [3; 4].

Poststroke dementia occurs approximately in 20 % of patients, although in majority of cases mild cognitive impairment is observed [3]. Stroke patients often also have anamnesis of chronic brain ischemia and cognitive decline [3]. Thereby neurodynamic disorders are prevalent: attention deficit, short-term memory impairment, slowness of psychic processes and increased fatigue ability during mental activity.

Cognitive impairment in stroke can evolve either due to infarction in "strategical" brain zone or due to widespread cerebrovascular disease or brain atrophic processes [3; 4].

Accordingly, elaboration of effective methods of early manifestation of cognitive impairment diagnosis, treatment and prophylaxis is one of priority tasks in neurology.

Currently progress in neuroimaging technology provides an opportunity to perform precise predominantly topical diagnosis of focal brain lesions. However, for assessment of brain structures functional status and objective evaluation of functional disorders intensity and cognitive impairment, including their preclinical stages, it is necessary to use other diagnostic tools.

Evoked potentials (EPs) registration is one of possible methods of brain functional status evaluation and it has a number of advantages: short session, stability of auditory EPs, independence of patient's psychical state and degree of his motivation, presence of affective and personality disorders (unlike with investigation by traditional psychometric scales). Important feature of EPs registration is a possibility to perform examination in conditions of passive stimuli acquisition, which makes it applicable for cases with difficult patient cooperation.

Mismatch negativity (MMN) is one of the components of the auditory event-related potential with peak latency of 100–250 ms, which reflects automatic process of deviation detection between two stimuli and characterizes neurodynamic processes in auditory cortex on the pre-attention stage. It is generated in response to the change of at least one physical stimulus feature, e. g. frequency, intensity and speech perception [5]. Psychophysiological function represented by MMN consists of involuntary capture of any changes in prolonged auditory stimulation and controlling of information transferring into consciousness. MMN generation indicates an opportunity to realize cognitive processes by means of involuntary attention mechanisms [6].

In cases of cerebral diseases MMN changes may outline deficit in auditory stimulus recognition accuracy, shortened lifetime of memory traces, deterioration involuntary attention switching. According to published data, decreased MMN amplitude and prolonged latency were described in patients with cognitive impairment due to various disorders (schizophrenia, neurodegenerative disorders, multiple sclerosis) [6–8].

MMN may be a non-specific electrophysiological correlate of cognitive dysfunction, in particular caused by cerebrovascular diseases. Nevertheless, there are few papers studying informational content of auditory EPs and MMN in stroke [5; 9; 10]. Consequently, current research aimed to investigate informational content of auditory EPs (acoustic brainstem and cognitive — MMN) in assessment of brain functional status and cognitive functions in patients with ischemic stroke (IS).

Methods

Research was performed for 22 patients (12 — with IS in carotid circulation, 10 — without cerebrovascular diseases) admitted to SPbGUZ "City hospital no. 15" of St. Petersburg. Stroke patients were hospitalized later than 4.5 hours after acute vascular event, none of them underwent thrombolysis. All the patients gave their informed written consent. MMSE scale, FAB, test with 10 words repetition and Schulte tables, traditionally used by clinicians, were applied for examination of cognitive functions. Spilberger-Khanin State-Trait Anxiety Inventory (STAI), Hospital Anxiety and Depression Scale (HADS) and Geriartric Depression Scale (GDS) were used for assessment of affective status [11].

All the patients underwent clinical and neurological examination, laboratory tests, neuroimaging (CT/ MRI), electrophysiological (ECG) and ultrasonic (USDG of brachiocephalic arteries) examination were consulted by physician and ophthalmologist. Neuroimaging and ultrasonic examination results were used for diagnosis verification and assessment of brain athrophic changes, hemodynamic characteristics and existence of atherosclerotic vascular disease of brachiocephalic arteries.

Clinical and neurophysiological examination, including registration of brainstem acoustic evoked potentials (BAEPs) and cognitive event-related potential (ERP) MMN was performed for 12 patients with IS in middle cerebral artery (MCA) circulation (9 — in left MCA circulation, 3 — in right MCA circulation). Mean age was 65.8±8.7 years old, men — 7, women — 5, mean scale by NIHSS — 3.45±1.44, by Rankin scale — 1.73±0.47. Control group consisted of 10 patients (mean age — 54.6±6.4 years old, men — 6, women — 4) without cerebrovascular diseases that underwent diagnosis and treatment of lumbaldorsopathy without acute pain stage.

Therewith EP method is based on signal coherent integration and averaging during repeated stimulus presentation, sample size of the present paper corresponds to current research in this field [9; 12].

Nihon Kohden MEB-9400 system (Japan) was used for registration of BAEPs. Ground electrode was attached on Fz site, reference — on Cz, active electrodes — on mastoid processes of temporal bones. Stimuli of "click" type (duration 0.1 ms, intensity 65 dB over patient's hearing level) were presented monaurally with 10 Hz frequency (two series of 1000 stimuli for each ear) [13].

MMN was registered using Neurovisor 24 EEG system (Neurobotics Ltd., Russia) in accordance with international guidelines for eliciting, recording, and quantifying event-relation potentials in clinical research [6].

MMN was studied in passive odd-ball paradigm, when deviant (rare) stimuli were presented in a sequence of standard (frequent) stimuli. In this paper standard and deviant stimuli differ by frequency of sinusoidal tone (1000 Hz and 900 Hz respectively). Probability of deviant stimulus presentation was 0.20, quantity — 150; quantity of standard stimuli — 450; interstimulus interval — 500 ms; stimulus duration — 50 ms.

EEG was registered at F3, Fz, F4, Cz, C3, C4 sites, where MMN is maximally pronounced [6], and at mastoid processes with reference electrode placed on the nose tip. Horizontal and vertical electro-oculogram was also recorded. Electrode impedances were kept below 5 kOhm. Event-related potential analysis was performed with WinEEG soft package (Mitsar, Russia) using independent component analysis. The sampling rate was 500 Hz. On-line filtering was applied using a 0.1–30 Hz band-pass filter.The MMN response was calculated by subtracting responses to the standard stimuli from those to the deviant ones. MMN amplitude was counted as the mean value in a 50 ms — window around individual peaks on the subtraction curve of event-related responses to the standard and deviant stimuli [14].

Statistical assessment of results was performed with Statistica-10 software package. Results are reported as a mean value and a standard deviation (M±σ). Mann-Whitney U-test was performed to confirm statistical significance between groups, Spearman correlation coefficient was used to study correlation. MMN parameters were assessed by repeated measures analyses of variance (ANOVA) with two-factor model in each group with *Stimulus Type* (two levels: standard vs. deviant), *Electrode Site* (eight levels: F3, Fz, F4, Cz, C3, C4, left and right mastoids) as within-subject factors followed by post-hoc tests. For comparison of mean MMN amplitude between groups two-factor model with factors *Group* (two levels: stroke vs. control) and *Electrode Site* (eight levels: F3, Fz, F4, Cz, C3, C4, left and right mastoids) was used.

Data was considered statistically significant when p-level value was below 0.05.

Results

Analysis of clinical and neurological examination of stroke patients revealed motor aphasia in 5 (42 %) cases, 12 (100 %) — paresis (with muscle strength score from 2 to 4), 12 (100 %) — signs of central paresis of mimic muscles, 3 (25 %) — sensitive deficit, 2 (17 %) — oral automatism symptoms, 4 (33 %) — light coordination deficit.

According to neuroimaging data, 92 % of patients in stroke group had evidence of atrophic processes predominantly in frontal areas and 50 % had substitutive hydrocephalus. Ultrasonic examination revealed atherosclerotic vascular disease in 67 % patients in stroke group.

Results of cognitive functions and affective status testing are listed in Table 1. Patients with stroke (group 1) reported lower MMSE and FAB scores, remembering of fewer words in 10 words repetition test and longer mean working time with Schulte tables as compared to control group.

Comparison of affective status revealed no significant differences between groups. However, moderate trait anxiety was observed in patients with IS, other tests were normal.

BAEPs and MMN examination results are listed in Table 2. Prolonged peak latency of wave V and increased interpeak intervals III–V on both sides and I–V ipsilaterally were recorded *in patients with stroke in carotid circulation* as compared to control group. Event-related potentials for the standard and deviant stimuli in patients with stroke are shown on Fig. 1, in control group — on Fig. 2. For comparison of MMN waves between groups see Fig. 3.

MMN research performed with repeated measures ANOVA revealed that mean amplitudes of standard and deviant ERPs were statistically different with a significant main effect of factor *Stimulus Type* (deviant vs. standard; df = 1, F = 12.07, p = 0.025 and df = 1, F = 65.07, p = 0.0012, respectively); interaction of factors *Stimulus Type * Electrode Site* was also significant(df = 7, F = 4.64, p = 0.001). Furthermore, three patients with stroke had no MMN wave (ERP responses to the standard and deviant stimuli were very similar).

In case of mean amplitude comparison statistically significant differences were observed in factors *Group* (df = 1, F = 6.79, p = 0.028) and *Electrode Site* (df = 7, F = 37.67, p < 0.0001), indicating a weaker MMN response in patients with stroke.

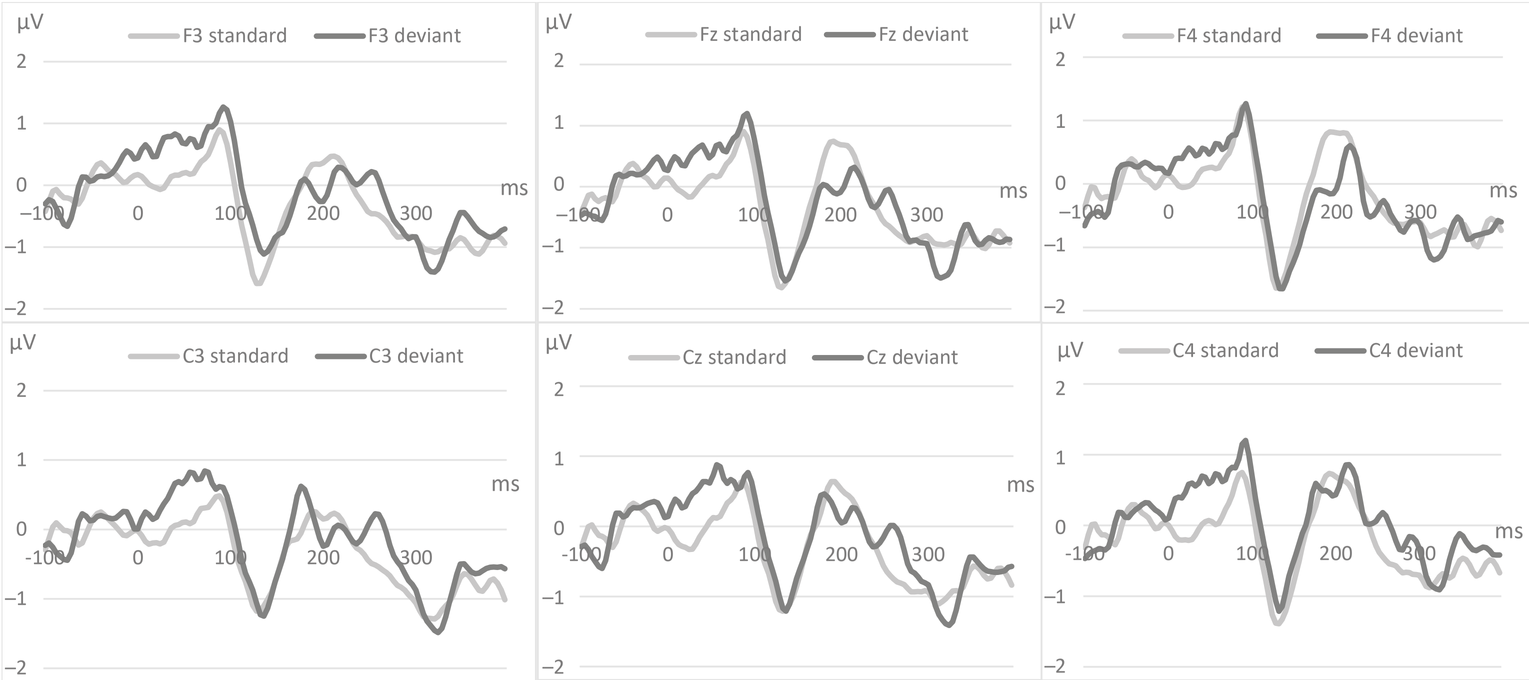

Fig. 1. ERPs for standard and deviant stimuli in patients with stroke.Only light difference of EPPs to standard and deviant stimulus is observed in 100–250 ms interval at frontal and central sites Signal polarity inversion at mastoid sites is registered.

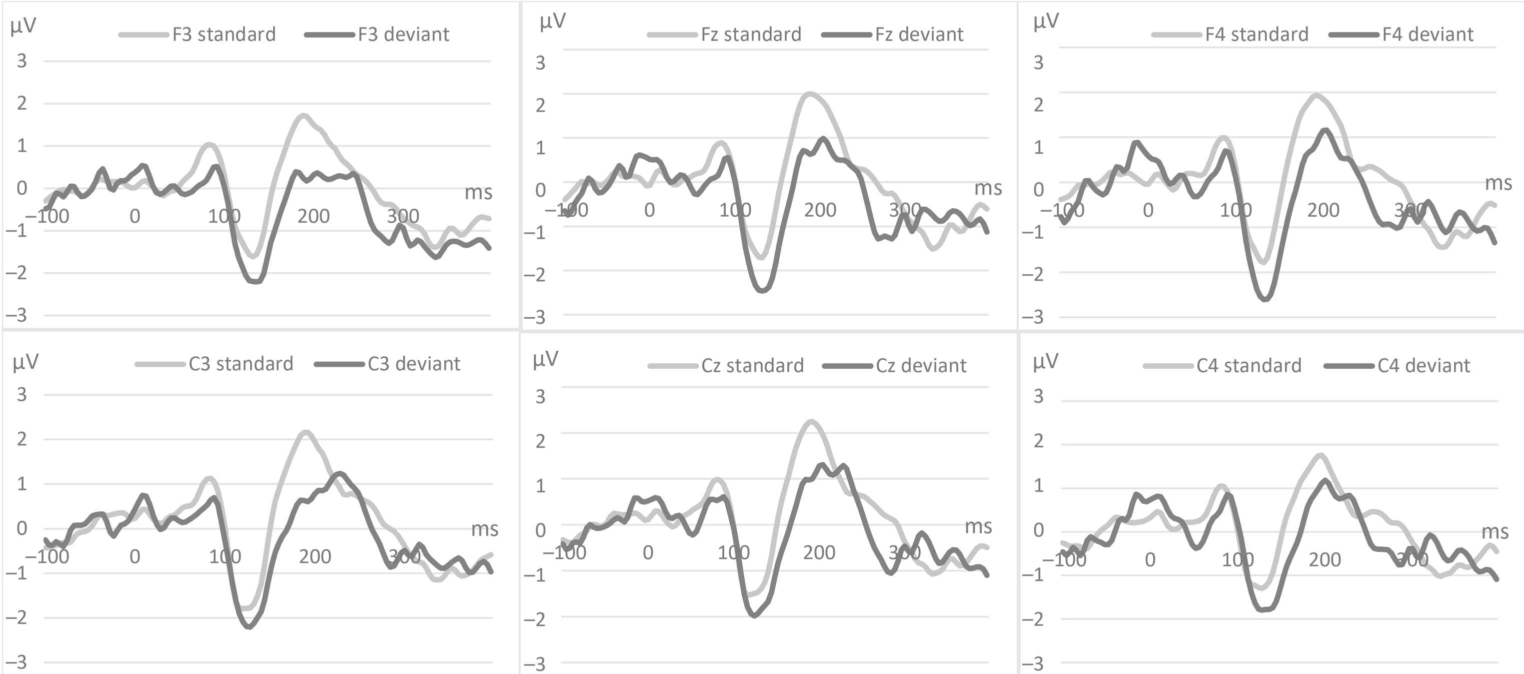

Fig. 2. ERPs for standard and deviant stimuli in patients of control group.Clear difference of EPPs to standard and deviant stimulus is observed in 100–250 ms interval at frontal and central sites. Signal polarity inversion at mastoid sites is registered that is typical for MMN.

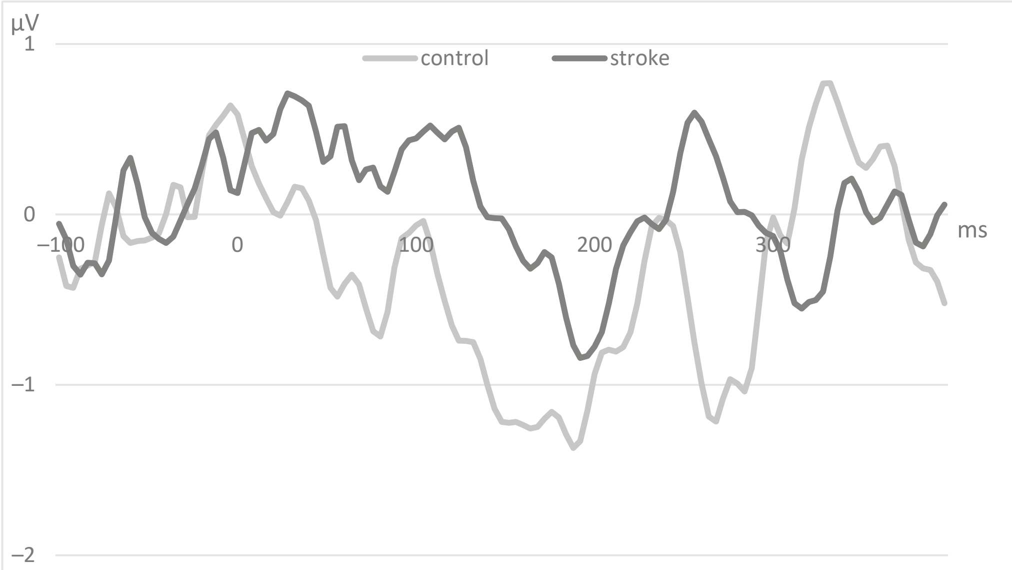

Fig. 3. MMN wave at Fz site in control group and patients with stroke. Mean MMN amplitude is larger in control group.

Table 1. **Results of cognitive function and affective status testing**

Index	**Group 1 (stroke)**	**Group 2 (control)**
Results of cognitive function testing		
MMSE (score)	25.83±1.85***	29.38±0.92
FAB (score)	14.33±2.23***	17.50±0.53
10 words repetition test (number of words)		
third repetition	6.08±1.31**	8.00±1.60
fifth repetition	7.25±1.54**	9.38±0.92
delayed repetition	5.75±2.26**	8.50±1.07
Schulte tables (mean time, s)	72.02±11.84***	42.40±6.49
Results of affective status testing		
GDS (score)	3.09±1.38	4.50±3.83
HADS (score)		
anxiety scale	4.75±2.87	6.60±4.98
depression scale	4.75±1.67	4.80±2.77
STAI (score)		
state anxiety	27.44±4.53	29.17±7.22
trait anxiety	43.33±11.00	45.83±12.61

Note: * — statistical significance $p < 0.05$; ** — $p < 0.01$;*** — $p < 0.001.467$. Results are reported as a mean value and a standard deviation ($M \pm \sigma$).

Table 2. **BAEPs and MMN results**

Index	Group 1 (stroke)	Group 2 (control)	Index	Group 1 (stroke)	Group 2 (control)
BAEPs, latency (ms)			BAEPs, interpeak interval (ms)		
Left wave I	1.86±0.25	1.93±0.16	Left I–III	2.17±0.30	2.01±0.15
Left wave III	4.03±0.29	3.96±0.17	Left I–V	4.57±0.39**	3.99±0.30
Left wave V	6.43±0.39*	5.91±0.28	Left III–V	2.40±0.44*	1.95±0.28
Right wave I	1.92±0.22	1.84±0.15	Right I–III	2.00±0.39	2.08±0.17
Right wave III	3.96±0.34	3.92±0.20	Right I–V	4.44±0.48	4.10±0.23
Right wave V	6.37±0.36**	5.83±0.27	Right III–V	2.43±0.50*	1.91±0.24
BAEPs, amplitude (μV)			MMN, amplitude (μV)		
Left wave V	0.24±0.16*	0.39±0.17	Fz	–1.06±0.45	–1.20±0.49
Right wave V	0.48±0.28	0.39±0.17	Cz	–0.66±0.48*	–1.10±0.47
			F3	–1.05±0.52	–1.15±0.35
MMN peaklatency (ms)			F4	–1.21±0.64	–1.14±0.47
	*180±31**	*162±18*	C3	–0.61±0.57*	–1.18±0.27
			C4	–0.74±0.53	–0.97±0.40

N o t e : * — statistical significance $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$. Results are reported as a mean value and a standard deviation ($M \pm \sigma$).

Also mean peak latency difference was statistically significant with stroke patients having prolonged MMN latency as compared to control group ($p < 0.05$).

In patients with stroke in left MCA circulation prolonged interpeak interval I–V ipsilaterally correlated with MMN amplitude decrease at Fz site ($R = -0.90$, $p < 0.05$) and prolonged interpeak interval III–V ipsilaterally correlated with MMN amplitude decrease at F3 and Cz sites ($R = -0.90$, $p < 0.05$).

In control group BAEPs were normal. Here with interconnection of interpeak intervals I–III and III–V with MMN amplitude at Cz site was found ($R = -0.90$, $p = 0.037$).

No significant correlations were found between lesion size (according to neuroimaging data) and changes of BAEPs or MMN parameters.

Discussion

It is known that any type of psychical activity needs a proper action of functional units, which have multilevel hierarchical structure including horizontal and vertical interactions [15].

Results of BAEPs research pointed out functional changes in patients with stroke in carotid circulation, concerning predominantly the first functional unit (the unit for regulating tone or waking) and the second functional unit (the unit for obtaining, processing and storing information) according to the conception of the three principal functional units of the brain by A. R. Luria [15].

Revealed prolongation of the interpeak interval I–V characterizes changes in conduction velocity in the brainstem in general, and prolongation of the interpeak interval

III–V and wave Vpeak latency indicates on functional impairments on the ponto-mesencephalic level [10; 13; 16].

In case of convincing clinical evidence of vertebrobasilar deficit absence in tested patients, we may speak about functional brainstem disorders associated with hemispheric lesions due to stroke.

Change of MMN parameters in stroke (prolonged peak latency, decreased difference in ERPs for the standard and deviant stimuli) points at dysfunction of the automatic process of deviant detection between two stimuli. It happens consequent on ischemia of brain areas responsible for MMN generation — auditory cortex, which provides sensory memory traces functioning and deviance tracing, and prefrontal area liable for comparison procedure (prognostic coding) and automatic attention shift during changing auditory stimulation [8; 17]. These results provide evidence of involvement of the second functional unit of the brain by A. R. Luria.

According to published data, MMN generation needs normal functioning of NMDA-receptors, which play crucial role in synaptic plasticity. Dysfunction of NMDA-receptors may be revealed, in particular, by abnormalities of memory traces formation and prognostic coding that are fundamental for MMN generation [8; 17; 18]. Therefore, MMN may reflect functional status of NMDA-receptors and characterizes brain plasticity.

Poor correlation of MMN parameters with neuropsychological testing results partially correlates with other research works, which found no correlations between MMN parameters and MMSE scores in patients with mild cognitive impairment and Alzheimer's disease [19].

Conclusions

1. According to results of MMSE, FAB, test of 10 words repetition and Schulte tables, patients with ischemic stroke in carotid circulation demonstrated cognitive impairment as compared to control group.
2. BAEPs research patients with ischemic stroke in carotid circulation revealed brainstem functional changes concerning predominantly the first functional unit of the brain (the unit for regulating tone or waking) by A. R. Luria.
3. Patients with ischemic stroke in carotid circulation demonstrated increased peak latency and decreased amplitude of cognitive ERP MMN. That indicates decline in auditory discrimination accuracy, shortened lifetime of memory traces, deficit in involuntary attention shift and testifies cognitive impairment with involvement of the second functional unit of the brain (the unit, that according A. R. Luria, is responsible for obtaining, processing and storing information).
4. Complex investigation of BAEPs and MMN may serves as informative method in assessment of brain functional status in patients with stroke in carotid circulation and can be applied in advanced functional diagnosis of brainstem structures and pre-attentional information processing, which is important component of cognitive functions.

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